REMARKS

Claims 1-38 and 40-43 are pending and under examination in this application. New claims 44-50 have been added, support for which can be found in the specification including, for example, at page 12, lines 25-30. Claim 28 has been amended to correct an obvious error. Accordingly, the amendments do not raise any issues of new matter and entry of the amendments is respectfully requested. Following entry of the amendments claims 1-38 and 40-50 will be under examination.

Applicants have reviewed all grounds of rejection issued in the Office Action mailed February 21, 2006, and respectfully traverse for the reasons that follow.

As a preliminary matter, with respect to claim interpretation, the Office states that Applicants appear to be in agreement with the Examiner's claim interpretation involving multimeric complexes. Because Applicants' interpreted the Office's previous description to be unclear, in part, Applicants' neither agree nor disagree with this statement. Rather, Applicants maintain that their previous description in the Response filed December 19, 2005, to be their understanding of the claim terms with respect to this issue.

Rejections Under 35 U.S.C. § 103

Claims 1-16, 22-27 and 31-42 stand rejected under 35 U.S.C. § 103(a) as being obvious over Rothberg et al., U.S. Patent No. 6,274,320, in view of Walt et al., U.S. Patent No. 6,327,410. In maintaining this ground of rejection, the Office attempts to distinguish Applicants' argument that Rothberg et al. teaches away from combining their pyrophosphate sequencing method with microspheres by alleging that Walt's description of immobilizing beads in an array provides the necessary motivation for use in pyrophosphate sequencing and provides a solution to the problem of bead loss during washing reported by Rothberg et al. Applicants will address below each of the apparent distinctions alleged by the Office.

Beginning with the alleged motivation to combine immobilization of beads in an array with the pyrophosphate sequencing of Rothberg et al., Applicants respectfully remind the Office that simply a description of a claimed element does not provide the proper motivation for its combination with a description in another reference absent some teaching, suggestion or

motivation to do so. This requirement prevents the use of the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability, which is the essence of hindsight. *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004).

The Office asserts that the description of bead immobilization in an array provides a solution to the problem of bead loss during washing when beads are used in the pyrophosphate sequencing method referenced in Rothberg et al. allegedly because the method referenced by Rothberg et al. used "beads suspended in a solution, without any support to rest on." Office Action, page 3, second paragraph and page 4, second paragraph.

Applicants fail to discern this attempt to distinguish Rothberg's teaching away from the use of a solid support such as beads in combination with pyrophosphate sequencing. First, Rothberg et. al. does not describe that the beads used in the described solid phase sequencing were "suspended in a solution." Rather, Rothberg et al. states that washes were performed "using streptavidin-coated magnetic beads as a solid support" (col. 21, lines 29-30). Hence, the Office's alleged distinction based on beads in solution appears to be unsupported by the description in Rothberg et al.

Second, the Office's alleged distinction over the teaching away described in Rothberg et al. appears to be further unsupported because the description relates to the use of magnetic beads, which do become supported by a substrate. Magnetic beads are affixed to a substrate generally through application of an externally applied magnetic force which causes the beads to rest on the bottom or sides of a test tube. Therefore, one skilled in the art would have been led to believe that immobilization of beads in an array does not solve the problem reported by Rothberg because the magnetic beads used in the earlier studies did have a support to rest on. Namely, the beads rested on, for example, the bottom of the test tube rather than in an organized array. Similarly, the same also would be correct if non-magnetic beads were to be used. Such solid particles would rest on the bottom of a test tube.

Finally, Applicants also fail to discern any distinction between suspending the beads in a test tube to perform a wash compared to passing a wash solution over the beads when they are resting on an array surface. In both instances, solution is passed over the solid support containing an attached nucleic acid. Hence, the undesirable results reported by Rothberg et al. do not appear to be solved by a description to organize the solid support into an array. Therefore, Rothberg's concerns

that magnetic beads are washed away is relevant to any combination of references alleged to provide beads resting on a support.

Thus, Applicants' remarks that Rothberg et al. teaches away from any teaching, suggestion or motivation to combine the pyrophosphate sequencing with microspheres remain applicable because Rothberg et al. explicitly point to reported problems associated with the use of pyrophosphate sequencing in combination with a solid support. The Office's purported distinction fails to address this problem because bead washing will occur whether the beads are processed in solution or on a support. In contrast, Applicants' conclusion that, according to Rothberg et al. combination of pyrosequencing with microspheres was undesirable, limited and inapplicable to pyrophosphate sequencing strategies is support by the descriptions in Rothberg et al. at, for example, column 21, lines 14-34, and as set forth in the record.

The Office further alleges that Rothberg et al. describe that different approaches can be used to decrease the distance between an immobilized primer site in order to distinguish released pyrophosphate (PPi) molecules from each other. In this regard, the Office cites to a passage that references Michael et al., implying that the cited passage and the Michael et al. reference provide the proper motivation to combine Rothberg et al. with Walt et al. The cited passage is at column 28, lines 24-32, of Rothberg et al., which describes the use of spatial-geometry and uniform cavities in pyrophosphate sequencing to physically prevent lateral diffusion of released PPi. This description does not appear to be directed to immobilization of nucleic acids on beads for detecting released PPi within a common reaction chamber as is claimed by the invention. Rather, and as apparently indicated in the Office Action, the cited description in Rothberg et al. focuses on the use of cavities as separate reaction chambers for each pyrophosphate sequencing reaction. For the Office's convenience, the full paragraph beginning at column 28, line 24 is quoted below:

> A fifth, and preferred, methodology to allow a decrease in the distance between individual anchor pads, is to conduct the pyrophosphate sequencing reaction in a spatial-geometry which physically-prevents the released PPi from diffusing laterally. For example, uniform cavities, which are generated by acid-etching the termini of optical fiber bundles, may be utilized to prevent such lateral diffusion of PPi (see Michael et al., 1998. Randomly Ordered Addressable High-Density Optical Sensor Arrays *Anal. Chem.* 70:1242-1248). In this embodiment, the important variable involves the total diffusion time for the PP; to exit a cavity of

> height h, wherein h is the depth of the etched cavity. This diffusion time may be calculated utilizing the equation: $2D_{\rho}t=h^2$. By use of the preferred pyrophosphate sequencing reaction conditions of the present invention in the aforementioned calculations, it may be demonstrated that a cavity 50 μm in depth would be required for the sequencing reaction to proceed to completion before complete diffusion of the PPi from said cavity. Moreover, this type of geometry has, the additional advantage of concomitantly reducing background signal from the released PPi from adjacent anchor pads. In contrast to use of a "chip" based geometry, wherein the required sequencing reagents are "flowed" over the surface of the solid support matrix (i.e., the anchor pads), delivery of the various sequencing reagents in acid-etched optical fiber bundle embodiment is performed by immersion of the acid-etched cavities, alternately, into dNTP/APS/sulfurylase reagents and then, subsequently, into the apyrase reagents to facilitate the degradation of any remaining dNTPs.

Col. 28, lines 24-52 (emphasis added).

As shown above, Rothberg et al. describes the method of using acid-etching to generate cavities in order to prevent lateral diffusion of PPi. In particular, Rothberg describes that pyrophosphate sequencing reactions can be performed in a spatial geometry using acid-etched cavities that physically prevent lateral diffusion of released PPi. A calculated cavity depth of 50 μm is described as being sufficient to accomplish this goal. This description in Rothberg et al., and citation to Michael et al., makes no mention of combining microspheres with pyrophosphate sequencing. Rather, Michael et al. is referenced by Rothberg for its description to a method of producing cavities by acid-etching. Therefore, the cited passage does not teach or suggest placing beads in wells nor does it describe the microbead arrays of Walt et al. because it is entirely directed to the method of acid-etching cavities.

The Office additionally cites to column 27, lines 7-13, and lines 42-46, allegedly for further support that Rothberg et al. describe approaches that can be used to decrease the distance between immobilized primer sites. Applicants respectfully point out that all four of the approaches described at column 27, lines 42 through column 28, line 23, are hypothetical because they are based on theoretical calculations. Moreover, two of the approaches point out disadvantages to reducing the theoretical distance. For example, the remainder of the paragraph cited by the Office (col. 27, lines 42-46) reads:

> One approach is to detect only the early light, although this has the disadvantage of losing signal, particularly from DNA sequences which possess a number of contiguous, identical nucleotides.

Col. 27, lines 46-49 (emphasis added). Because the possible approaches outlined by Rothberg et al. are theoretical and include at least two drawbacks for using solid supports, Applicants submit that such descriptions fail to provide the proper motivation to combine Rothberg et al. with Walt et al.

Therefore, Applicants' statements in their previous response are still applicable. Namely, none of the theories or calculations beginning at column 21, line 11 "describe or suggest combining any pyrophosphate sequencing method with microspheres." Response filed December 19, 2005, paragraph bridging pp 11-12. As pointed out above, Walt's mere mention of beads in an array fail to provide the proper teaching, suggestion or motivation to combine a solid support such as microspheres with a method of pyrophosphate sequencing. Further, the descriptions in Rothberg et al. cited by the Office at column 28, lines 24-52, or those at column 27, 7-13, and lines 42-49, also fail to provide the proper teaching, suggestion or motivation to combine Rothberg's sequencing method with a solid support because they lack any mention of using microspheres and they do not suggest how to overcome the disadvantages he reports using microspheres if one were to, nevertheless, employ microspheres in pyrophosphate sequencing. Therefore, Rothberg teaches away from using a solid support such as beads in combination with pyrophosphate sequencing methods. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 18, 19, 28-30 and 43 stand rejected under 35 U.S.C. § 103(a) as being obvious over Rothberg et al., Walt et al., Nyren et al., WO 98/13523, and the Stratagene catalog (1998, p39). The Office appears to maintain this ground of rejection based on its rebuttal of Applicants' arguments over Rothberg et al. As pointed out above, Rothberg et al. teaches away from combining pyrophosphate sequencing with microspheres. Applicants have shown above that none of the citations in either the primary or secondary reference teach, suggest provide the proper motivation to combine pyrophosphate sequencing with a solid support such as a microsphere. Absent such a teaching, suggestion or motivation, the invention as claimed is not

rendered obvious over the cited references. Therefore, Applicants respectfully request withdrawal of this ground of rejection.

The Office further maintains the rejections of claims 17, 20 and 21 as allegedly obvious allegedly because these rejections were not specifically addressed in Applicants' previous response. Applicants respectfully point out that the rejected claims are dependent on one or more independent claims. Therefore, claims 17, 20 and 21 contain all the limitations of the base claim from which they depend. Applicants have addressed the independent claims above.

Newly added claims 44-50 require that the common chamber comprises a flow cell. Applicants respectfully submit that the claims are not obvious over the cited references because the combination of references does not teach or suggest the use of a flow cell as claimed.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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